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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,777	04/09/2004	Winston T.K. Cheng	MR2723-365	8832

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,777	CHENG ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-34* is/are pending in the application.

4a) Of the above claim(s) *32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18, 35 and 36 have been canceled. Claims 19-34 remain pending.

Applicant's arguments filed 12-26-07 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 32-34 submitted 6-29-07 remain directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The milk (claims 32-34) is patentably distinct from the transgenic and method of making the transgenic. Inventions are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product, and the species are patentably distinct (MPEP § 806.05(j)). In the instant case, the intermediate product (transgenic) is deemed to be useful as food and the inventions are deemed patentably distinct because there is nothing on this record to show them to be obvious variants. Claims 32-34 do not clearly set for the milk collected has the FVIII protein.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-34 remain withdrawn from

consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 19-31 remain under consideration as they relate to transgenics and methods of making transgenics.

Claim Objections

The objection to claims 20-24 has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

Claim 27 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection regarding the phrases "mammary gland-specific signal peptide" and "lacking innate signal peptide" in claim 19 as being new matter have been withdrawn in view of the amendment.

The rejection regarding the use of "a" in claims 20-24 has been withdrawn in view of the amendment.

The rejection regarding the phrase "as the non-human transgenic mammal" in claim 28 has been withdrawn in view of the amendment.

The phrase "up to about 50 mg" (claim 27) remains rejected under new matter. The phrase does not have support in originally claim 16, which is limited to an amount

that "can reach 50 mg", which does not have the same scope. "About" increases the scope beyond "up to 50 mg" as originally described.

Indefiniteness

Claim 27 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claim 19 regarding the phrase "lacking its innate signal peptide" has been withdrawn in view of the amendment.

The rejection regarding claim 24 has been withdrawn in view of applicants' arguments.

The rejection regarding claim 28 has been withdrawn in view of the amendment.

Claim 27 remains indefinite because the metes and bounds of what applicants consider "up to about 50 mg" cannot be determined. The amendment does not clarify the metes and bounds of the claim.

Rejections - 35 USC § 103

Claims 19-21, 24-26 and 28-31 remain rejected and claim 27 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001).

Chen made a transgenic mouse comprising a vector encoding 7.2 kb of hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid bovine a-LA signal peptide sequence (pg 258, col. 2, first full paragraph; paragraph

bridging pg 258-259). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13 and encoded by SEQ ID NO: 1. The mouse was made by introducing the transgene construct (i.e. expression cassette) into an embryo, implanting the embryo into a recipient female, allowing the embryo to develop to term, and testing the resulting offspring and identifying mice that secreted hFVIII in milk by RT-PCR and analysis of the milk for protein (paragraph bridging columns 1 and 2 of pg 263). Chen did not delete the B-domain of hFVIII.

However, Soukharev suggested making transgenic mammals expressing B-domain deleted FVIII to improve yield of FVIII (pg 241, paragraph bridging columns 1 and 2). "[A]nother approach to improve recombinant FVIII molecule is to introduce modifications to improve its effective secretion from FVIII-expressing cell" (page 239, col. 1, paragraph 1, lines 1-4) and that "removal of the B domain...was found to dramatically improve the yield of FVIII" (page 237, col. 2, lines 3-6). Soukharev taught "an attractive possibility to increase the yield of rFVIII is to produce a biologically active form of FVIII by coexpressing its heavy and light chains" (page 239, paragraph 2, line 1 to col. 2, line 2). The phrase "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" encompasses any B-domain deleted hFVIII protein of SEQ ID NO: 15. The nucleic acid sequence encoding the B-domain deleted hFVIII taught by Soukharev encodes "a B-domain deleted hFVIII polypeptide of SEQ ID NO: 15" as in claim 24. Without evidence to the contrary, the B-domain deleted hFVIII taught by Soukharev inherently produces a hFVIII comprising a light chain (A3-C1-C2 domain) and a heavy chain (A1-A2 domain) operably linked by a junction as in claim 25.

Thus, it was obvious to those of ordinary skill in the art at the time of filing to make a transgenic mouse encoding hFVIII as taught by Chen, wherein the hFVIII had a deletion in the B-domain as taught by Soukharev. Soukharev provides motivation on pg 241, lines 1-5. Those of skill would have a reasonable expectation of successfully improving the yield of FVIII as suggested by Soukharev because results in vitro improved the yield (pg 237, "Genetic engineering to improve the yield of recombinant FVIII). Lubon provides further evidence that fragments of hFVIII could be made in a non-human transgenic animal (claim 1 of Lubon).

Claim 27 is included because "producing up to about 50 mg" per liter as newly amended encompasses expressing any amount up to 50 mg/l (µg/ml) and because Chen taught an average concentration of hFVIII of 20 µg/ml. The phrase "up to 50" µg/ml encompasses 20 µg/ml taught by Chen. Claim 27 is also included because Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "about" 50 µg/ml as claimed.

Response to arguments

Please separate arguments for each obviousness rejection. While arguments for one may be referred to or copied, the arguments cannot be combined.

Applicants argue the prior art does not provide a reasonable expectation of success. Applicants' argument is not persuasive. Applicants' argument is unfounded. Furthermore, Chen and Soukharev both obtained functional expression of full length hFVIII in transgenics and B-domain deleted FVIII in vitro.

Applicants argue the combination of elements described by Chen and Soukharev gave unexpected expression levels of FVIII. The second Declaration by Chen provides a Table comparing full-length FVIII and B-domain deleted FVIII expression in transgenics. Applicants' arguments are not persuasive. Chen taught an average concentration of hFVIII of 20 µg/ml, which meets the limitation of "up to about 50 mg" per liter as claimed (claim 27). Furthermore, Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "about" 50 µg/ml as claimed. The Table in the second declaration fails to take into account the increase in expression described by Soukharev when the B-domain is deleted. Finally, the claims do not require expression of B-domain deleted FVIII beyond that expected from the combined teachings of Chen and Soukharev. The combination of elements described by Chen and Soukharev did not provide unexpected expression levels of FVIII when compared to claim 19 and meet the levels specifically set forth in claim 27.

Applicants argue the combination of elements described by Chen and Soukharev gave unexpected clotting activity of FVIII. The second Declaration by Chen provides Table 2 which states the activity of B-domain deleted FVIII in transgenics was 10-15% as compared to 5-10% for full-length FVIII described by Chen. Applicants conclude the increase in activity observed when the B-domain of FVIII was deleted was unexpected. Applicants' arguments are not persuasive. Applicants' analysis fails to compare the activity of transgenics claimed to the expected activity of transgenics made by the combined teachings of Chen and Soukharev. Applicants merely provide the expected

activity of Chen alone, not the expected activity of the combined teachings of Chen and Soukharev. Furthermore, Soukharev cites Toole (PNAS, Aug. 1986, Vol. 83, pg 5939-5942) (see pg 237, col. 2, line 2) who taught activity was greater in B-domain deleted FVIII than wild-type (pg 5941, sentence bridging col. 1 and 2). Therefore, the increase in activity observed was expected. In the alternative, Soukharev also cites Pittman (Blood, 1993, Vol. 81, pg 2925-2935) (pg 237, col. 2, line 13) who taught activity was the same in B-domain deleted FVIII and wild-type. If so, the increase in activity observed was caused by the bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) (pg 5 of second declaration). The bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) are essential to obtain the increase in FVIII activity observed by applicants. Claims 22 and 23 require the construct comprises a bovine αS1-casein signal sequence, but the claims are not included in this rejection. Applicants have not shown the increase in activity observed was unexpected as compared to the combined teachings of Chen and Soukharev or correlates properly to the claims rejected. Accordingly, applicants' arguments regarding unexpected FVIII activity are not persuasive.

Applicants argue the construct used by applicants was different than the one taught by the combined teachings of Chen and Soukharev. Applicants' argument is not persuasive. The construct used in claim 19 is not different than the construct used by the combined teachings of Chen and Soukharev. The construct used by applicants required a bovine αS1-casein signal sequence as in claims 22 and 23, which have not been included in the rejection.

Claims 19-26 and 28-31 remain rejected and claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen (Transgenic Research, 11:257-268, 2002) in view of Soukharev (Blood Cells, Molecules and Diseases, 28:234-248, 2002) and supported by Lubon (US Patent 6,255,554, Issued July 3, 2001) as applied to claims 19-21, 24-31 above, and further in view of DeBoer (US Patent 5,633,076, Issued May 27, 1997).

The combined teachings of Chen and Soukharev taught making a transgenic mouse comprising a vector encoding B-domain deleted hFVIII coding region operably linked to the 2.0 kb bovine a-LA promoter and 19 amino acid signal peptide sequence (Chen - pg 258, col. 2, first full paragraph; paragraph bridging pg 258-259; Soukharev - pg 241, paragraph bridging columns 1 and 2; page 239, col. 1, paragraph 1, lines 1-4; page 237, col. 2, lines 3-6; page 239, paragraph 2, line 1 to col. 2, line 2; see 103 rejection above). The 19 amino acid leader sequence of Chen is the 19 amino acid signal peptide of SEQ ID NO: 13. The mouse secreted hFVIII in milk (paragraph bridging columns 1 and 2 of pg 263). The combined teachings of Chen and Soukharev did not teach replacing the 19 amino acid a-LA signal peptide of SEQ ID NO: 13 with the 15 amino acid α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2).

However, DeBoer taught a nucleic acid construct comprising various nucleic acid elements for the optimization of producing recombinant protein in the milk of transgenic animals, said recombinant protein including FVIII (col. 7, line 12) including the alpha S1

casein secretion signal peptide (col. 7, lines 18-27). DeBoer also taught using the alpha-lactalbumin, whey acidic protein, beta-casein and alpha S1 casein (col. 2, line 53 to col. 3, line 5).

Thus, it was obvious to make a transgenic mouse encoding B-domain deleted hFVIII operably linked to the as taught by the combined teachings of Chen and Soukharev, wherein the a-lactalbumin signal peptide of SEQ ID NO: 13 was replaced with the α-S1 casein signal peptide of SEQ ID NO: 14 (encoded by SEQ ID NO: 2). One of ordinary skill in the art would have been motivated to use the α-S1 casein signal peptide instead of the α- lactalbumin signal peptide to increase secretion of hFVIII into the milk. Those of skill would have a reasonable expectation of successfully swapping signal peptides in view of the teachings of DeBoer. Lubon provides further evidence that signal peptides could be readily swapped to increase secretion into the milk of a non-human transgenic animal. Lubon states the "[i]mportant to the present invention are regulatory sequences that direct secretion of proteins into milk and/or other body fluids of the transgenic animal. In this regard, both homologous and heterologous regulatory sequences are useful in the invention. Generally, regulatory sequences known to direct the secretion of milk proteins, such as either signal peptides from milk proteins or the nascent target polypeptide, can be used..." (col. 6, lines 45-52).

Claim 27 is included because "producing up to about 50 mg" per liter as newly amended encompasses expressing any amount up to 50 mg/l (µg/ml) and because Chen taught an average concentration of hFVIII of 20 µg/ml. The phrase "up to 50" µg/ml encompasses 20 µg/ml taught by Chen. Claim 27 is also included because Chen

taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "about" 50 µg/ml as claimed.

Response to arguments

Please separate arguments for each obviousness rejection. While arguments for one may be referred to or copied, the arguments cannot be combined.

Applicants argue the prior art does not provide a reasonable expectation of success. Applicants' argument is not persuasive. Applicants' argument is unfounded. Furthermore, Chen and Soukharev both obtained functional expression of full length hFVIII in transgenics and B-domain deleted FVIII in vitro.

Applicants argue the combination of elements described by Chen, Soukharev and DeBoer gave unexpected expression levels of FVIII. The second Declaration by Chen provides a Table comparing full-length FVIII and B-domain deleted FVIII expression in transgenics. Applicants' arguments are not persuasive. Chen taught an average concentration of hFVIII of 20 µg/ml, which meets the limitation of "up to about 50 mg" per liter as claimed (claim 27). Furthermore, Chen taught an average concentration of hFVIII of 20 µg/ml and Soukharev taught deleting the B-domain would increase expression, which is equivalent to "about" 50 µg/ml as claimed. The Table in the second declaration fails to take into account the increase in expression described by Soukharev when the B-domain is deleted and fails to account for using the bovine αS1 casein signal peptide described by DeBoer. Finally, the claims do not require expression of B-domain deleted FVIII beyond that expected from the combined

teachings of Chen, Soukharev and DeBoer. The combination of elements described by Chen, Soukharev and DeBoer did not provide unexpected expression levels of FVIII when compared to claim 22 or 23 and meet the levels specifically set forth in claim 27.

Applicants argue the combination of elements described by Chen, Soukharev and DeBoer gave unexpected clotting activity of FVIII. The second Declaration by Chen provides Table 2 which states the activity of B-domain deleted FVIII in transgenics was 10-15% as compared to 5-10% for full-length FVIII described by Chen. Applicants conclude the increase in activity observed when the B-domain of FVIII was deleted was unexpected. Applicants' arguments are not persuasive. Applicants' analysis fails to compare the activity of transgenics claimed to the expected activity of transgenics made by the combined teachings of Chen, Soukharev and DeBoer. Applicants merely provide the expected activity of Chen alone, not the expected activity of the combined teachings of Chen, Soukharev and DeBoer. Furthermore, Soukharev cites Toole (PNAS, Aug. 1986, Vol. 83, pg 5939-5942) (see pg 237, col. 2, line 2) who taught activity was greater in B-domain deleted FVIII than wild-type (pg 5941, sentence bridging col. 1 and 2). Therefore, the increase in activity observed was expected. In the alternative, Soukharev also cites Pittman (Blood, 1993, Vol. 81, pg 2925-2935) (pg 237, col. 2, line 13) who taught activity was the same in B-domain deleted FVIII and wild-type. If so, the increase in activity observed was caused by the bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) (pg 5 of second declaration); however, only claims 22 and 23 require a bovine αS1-casein signal sequence and none of the claims require the S741-line to-L1643 recombinant splice site for the B-domain

deletion. The bovine αS1-casein signal sequence and new recombinant spliced site (S741-link to –L1643) are essential to obtain the increase in FVIII activity observed by applicants. Applicants have not shown the increase in activity observed was unexpected as compared to the combined teachings of Chen, Soukharev and DeBoer or correlates properly to the claims as broadly written. Accordingly, applicants' arguments regarding unexpected FVIII activity are not persuasive.

Applicants argue the construct used by applicants was different than the one taught by the combined teachings of Chen, Soukharev and DeBoer. Applicants' argument is not persuasive. The construct used in claims 22 and 23 is not different than the construct used by the combined teachings of Chen, Soukharev and DeBoer. The claims do not require the S741-line to-L1643 recombinant splice site for the B-domain deletion described in the second declaration by Chen in Table 3.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner